CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201635Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template for Trokendi XR (topiramate XR)
PMR # 2080-1

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA: Develop an age appropriate formulation of Trokendi XR (topiramate) extended-release capsules that can be used in children 1 month to less than 6 years old.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	MM//YYYY
Study/Clinical trial Completion Date:	MM//YYYY
Final Report Submission Date:	08/2015
Other:	MM//YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a deferred pediatric study under PREA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Trokendi is a capsule that can be administered once daily, but cannot be used in patients under 6 years of age because of difficulty swallowing a capsule of this size. PREA requires that the Sponsor attempt to develop an age appropriate formulation in this younger population with features similar to those of Trokendi XR.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop an age appropriate formulation of Trokendi XR (topiramate) extended-release capsules that can be used in children 1 month to less than 6 years old.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
This is not a study but a requirement under PREA to develop an age appropriate formulation.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Trokendi XR (topiramate XR)
PMR # 2080-2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA: A study to evaluate the pharmacokinetics (PK) and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, in children ages 2 years to less than 6 years with partial onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and/or Lennox-Gastaut syndrome (LGS), and evaluating bioavailability after administration once daily relative to bioavailability of the reference listed drug, Topamax, given twice daily.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	11/2015
Study/Clinical trial Completion Date:	11/2018
Final Report Submission Date:	05/2019
Other:	MM//YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a deferred pediatric study under PREA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Trokendi XR is a capsule that can be administered once daily, but cannot be used in patients under 6 years of age but because of difficulty swallowing a capsule of this size. PREA requires that the Sponsor attempt to develop an age appropriate formulation (see PMR 1) in this younger population with features similar to those of Trokendi XR (once daily dosing). The goal of this study is to evaluate the pharmacokinetics (PK) and safety of an age-appropriate formulation (see PMR 1) of Trokendi XR (topiramate) in children ages 2 years to less than 6 years of age under 6 years of age and evaluating bioavailability relative to bioavailability of the reference listed drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate the pharmacokinetics (PK) and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, in children ages 2 years to less than 6 years with partial onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and/or Lennox-Gastaut syndrome (LGS), and evaluating bioavailability after administration once daily relative to bioavailability of the reference listed drug, Topamax, given twice daily.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
PREA study

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template for Trokendi XR (topiramate XR)
PMR # 2080-3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA: A study to evaluate the PK and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	02/2016
Study/Clinical trial Completion Date:	02/2019
Final Report Submission Date:	08/2019
Other:	MM//YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a deferred pediatric study under PREA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Trokendi XR is a capsule that can be administered once daily, but cannot be used in patients under 6 years of age because of difficulty swallowing a capsule of this size. PREA requires that the Sponsor attempt to develop an age appropriate formulation (see PMR 1) in this younger population with features similar to those of Trokendi XR (once daily dosing). The goal of this study is to evaluate the PK and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☒ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate the PK and tolerability of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
A PREA study.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template for Trokendi XR (topiramate XR)
PMR # 2080-4

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA: An adequately controlled study to assess the efficacy and safety of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	11/2019
	Study/Clinical trial Completion Date:	11/2024
	Final Report Submission Date:	08/2025
	Other:	MM//YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a deferred pediatric study under PREA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Trokendi XR is a capsule that can be administered once daily, but cannot be used in patients under 6 years of age because of difficulty swallowing a capsule of this size. PREA requires that the Sponsor attempt to develop an age appropriate formulation (see PMR 1) in this younger population with features similar to those of Trokendi XR (once daily dosing). The goal of this study is to assess the efficacy and safety of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An adequately controlled study to assess the efficacy and safety of an age-appropriate formulation of Trokendi XR (topiramate) extended-release capsules, developed in PMR 2080-1, as adjunctive therapy in children ages 1 month to less than 2 years with partial onset seizures (POS).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
A PREA study.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY U YASUDA
08/15/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 201635	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Trokendi XR Established/Proper Name: Topiramate Dosage Form: Extended Release Capsules Strengths: 25mg, 50mg, 100mg, and 200mg		
Applicant: Supernus Pharmaceuticals, Inc.		
Date of Receipt: Original application: January 14, 2011 Class 2 resubmission: December 7, 2012 Class 1 resubmission: June 18, 2013		
PDUFA Goal Date: August 18, 2013	Action Goal Date (if different):	
Proposed Indication(s): 1. Monotherapy epilepsy: Initial monotherapy in patients (b) (4) with partial onset or primary generalized tonic-clonic seizures. 2. Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS) [Note: These are the same epilepsy indications as approved for Topamax and for the same patient populations except for the lower pediatric age; Topamax is approved for use in pediatric patients down to age 2. Topamax is also approved for the treatment of migraine. The applicant is not seeking this indication.]		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Topamax package insert NDA 20844 Topamax® Sprinkle Capsules NDA 20505 Topamax® Tablets	Non-clinical
Topamax package insert NDA 20844 Topamax® Sprinkle Capsules NDA 20505 Topamax® Tablets	Safety and efficacy

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The application contains CMC information and clinical pharmacology studies. A description (from Module 2.5.1.4 of the application) of the bridging study (Study 538P108) is below:

Study 538P108 compared topiramate levels in epilepsy patients after switching from an immediate-release formulation (TOPAMAX®) to the extended-release formulation of SPN-538T. The results from this study establish the equivalent bioavailability of the two formulations at steady state and validate the pharmacokinetic model used to simulate SPN-538T levels in epilepsy patients.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Topamax (topiramate) Tablets	20505	Y
Topamax (topiramate) Sprinkle Capsules	20844	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provided for a new extended-release dosage form. The RLDs are immediate-release products.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): There are numerous generic tablets as well as numerous generic capsules that are pharmaceutical alternatives.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): List is attached.

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

Note: Applicant doesn't explicitly cite this regulation but the application includes safety language previously protected by pediatric exclusivity which expired on June 22, 2013.

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☒ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 5,998,380; 6,503,884; 7,018,983; 7,498,311
Method(s) of Use/Code(s): U-598, U-598, U-723, U-955

Note: Applicant doesn't explicitly cite this regulation but does provide a statement (that is part of the patent certification) that they are not seeking approval for these uses.

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 7,125,560

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

Note: Applicant submitted patent certification stating that they would notify the sponsor (attached). Applicant submitted a patent amendment stating that patent holder was notified. (attached)

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): November 28, 2011

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

FDA Home[3] Drug Databases[4] Orange Book[5]

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020844 Product No 1 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020844	001	5998380	Oct 13, 2015			U - 598	
N020844	001	5998380*PED	Apr 13, 2016				
N020844	001	6503884	Oct 13, 2015			U - 598	
N020844	001	6503884*PED	Apr 13, 2016				
N020844	001	7018983	Oct 13, 2015			U - 723	
N020844	001	7018983*PED	Apr 13, 2016				
N020844	001	7125560	Mar 1, 2019			U - 766	
N020844	001	7125560*PED	Sep 1, 2019				
N020844	001	7498311	Oct 13, 2015			U - 955	
N020844	001	7498311*PED	Apr 13, 2016				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N020844	001	NPP	Jul 15, 2014
N020844	001	M - 54	Dec 22, 2012
N020844	001	PED	Jun 22, 2013

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Patent and Exclusivity Search Results from query on Appl No 020505 product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020505	001	5998380	Oct 13, 2015			U - 598	
N020505	001	5998380*PED	Apr 13, 2016				
N020505	001	6503884	Oct 13, 2015			U - 598	
N020505	001	6503884*PED	Apr 13, 2016				
N020505	001	7018983	Oct 13, 2015			U - 723	
N020505	001	7018983*PED	Apr 13, 2016				
N020505	001	7498311	Oct 13, 2015			U - 955	
N020505	001	7498311*PED	Apr 13, 2016				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N020505	001	NPP	Jul 15, 2014
N020505	001	M - 54	Dec 22, 2012
N020505	001	PED	Jun 22, 2013

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/s/

TAURA N HOLMES
08/14/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Memo

Date:	June 6, 2013
Reviewer:	Julie Neshiewat, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Trokendi XR (Topiramate) Extended-release Capsules 25 mg, 50 mg, 100 mg, 200 mg
Application Type/Number:	NDA 201635
Applicant:	Supernus Pharmaceuticals
OSE RCM #:	2012-1983

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1 INTRODUCTION

This review evaluates the revised labels and labeling for Trokendi XR (Topiramate) Extended-release Capsules, NDA 201635, received via e-mail on June 6, 2013 from the Applicant (Appendices A and B). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2011-3357 dated May 17, 2012 and OSE Review # 2012-1983 dated May 15, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling received via e-mail on June 6, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2011-3357 dated May 17, 2012 and OSE Review # 2012-1983 dated May 15, 2013.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling adequately address our concerns from a medication error perspective. DMEPA concludes that the revised labels and labeling are acceptable.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

12 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

JULIE V NESHIEWAT
06/06/2013

IRENE Z CHAN
06/06/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	May 15, 2013
Reviewer:	Julie Neshiewat, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Trokendi XR (Topiramate) Extended-release Capsules 25 mg, 50 mg, 100 mg, 200 mg
Application Type/Number:	NDA 201635
Applicant:	Supernus Pharmaceuticals
OSE RCM #:	2012-1983

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Contents

1 INTRODUCTION

This review evaluates the revised blister pack labeling and container labels for Trokendi XR (Topiramate) Extended-release Capsules, NDA 201635, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed proposed container labels and blister pack labeling in OSE Review # 2011-3357 dated May 17, 2012. During the previous review of proposed container labels and blister pack labeling, we noted that the capsules were difficult to remove from the blister packs. In some instances, the capsules were crushed as we attempted to remove them, and the layout of the capsules was confusing.

On May 2, 2012, DMEPA and the the Division of Neurology Products (DNP) held a teleconference with the Applicant to discuss our concerns with the blister packaging and to request that the Applicant conduct a usability study to verify that patients can access the medication. Since we identified concerns with the blister packaging and there is no evidence to support the usability of the blister packaging, DNP indicated that regulatory action would only be taken on the bottle configurations. On May 24, 2012, the Applicant was sent recommendations for the proposed container labels and blister pack labeling. On June 22, 2012, the Applicant and DMEPA reached an agreement for final container labels. The Applicant received a Tentative Approval Letter for the application on June 25, 2012.

On August 21, 2012, the Applicant submitted revised blister pack labeling, physical samples of the blister packaging, and a usability study protocol to IND 101670. After reviewing the blister pack samples, DMEPA and DNP agreed that the redesign of the blister packaging addressed our previous concerns regarding the layout of the capsules as well as the ability of patients to push out the capsules without crushing them. The Applicant was notified on September 6, 2012 that a usability study was no longer required with the redesigned blister packaging.

On February 27, 2013, the Applicant submitted another revised version of blister packaging to the NDA. An information request (IR) was sent to the Applicant on March 1, 2013 asking for their rationale for changing the blister packaging configuration and to ask for samples of the new blister pack. The Applicant responded that the (b) (4) features of the blister pack were re-evaluated and their new packager recommended the (b) (4) packaging. The FDA contacted the (b) (4) packager, (b) (4) to determine if other marketed products use the (b) (4) packaging, and if there have been any complaints or reports of error with the packaging. (b) (4) responded that another product, (b) (4) Capsules, was approved with the (b) (4) packaging, but the product has not been marketed yet. Per FDA request, die cut flats of the 30-count blister packs

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with artwork for each dose strength were submitted on March 18, 2013, and fully functional 30-count blister pack prototypes with a blank outer card containing active drug product for each dose strength were submitted on March 25, 2013.

As indicated above, on June 22, 2012, the Applicant and DMEPA reached an agreement for final container labels. Subsequently, the Applicant was advised by their packaging vendor to include a data matrix box for quality control and inventory purposes on the container labels. On April 15, 2013, the Applicant submitted revised container labels for all four strengths to include a data matrix box.

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Trokendi XR blister pack labeling, blister packaging, and container labels submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- (b) (4)
- Blister Pack Labeling: Retail 30-count submitted February 27, 2013 (Appendix B)
- Bottle Labels: Retail 100-count submitted April 15, 2013 (Appendix C)
- Samples of Blister Pack Labeling: Retail 30-count submitted March 18, 2013 and March 25, 2013 (No image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed Trokendi XR labels and labeling in OSE Review # 2011-3357 dated May 17, 2012. We looked at our previous review to ensure all our recommendations were implemented.

2.3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The proposed (b) (4) packaging by (b) (4) appears different from a majority of the currently marketed blister cards. The packaging (b) (4) . (b) (4) stated that another product, Capsules, was approved with the (b) (4) packaging, but the product has not been marketed yet. Therefore, there is no history of complaints or reports of error with the (b) (4) packaging. The instructions provided on the blister pack labeling

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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(b) (4)

Review of the revised blister pack labeling determined that the Applicant did not implement all of our previous recommendations, such as presenting the strength as "XX mg per capsule." In addition, we identified additional changes that should be made to the blister card labeling to improve readability, such as revising instructions from all upper case to title case.

The placement of the data matrix box on the container labels is on the side panel and away from the bar code. We find the revised container labels with the addition of the data matrix box acceptable.

3 CONCLUSIONS

DMEPA concludes that the revised container labels are acceptable; however, the proposed blister pack labeling can revised to improve the readability and prominence of important information on the labeling as well as add clarifying information to ensure proper use of the blister packaging.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

Comments to the Applicant

A. Blister Pack Labeling: (b) (4) Retail 30-count

Revise the statement (b) (4) to read similar to "Administer prescribed dose once daily. Please see package insert for dosage and other prescribing information."

B. Blister Pack Labeling: (b) (4)

(b) (4)

(b) (4)

C. Blister Pack Labeling: Retail 30-count

1. All presentations of strength on the blister pack should read "XX mg per capsule" inside of the highlighted circle.
2. Ensure that the panels containing drug product state the proprietary name, established name, and strength together.
3. Revise the instructions "SQUEEZE TABS HERE AND HOLD. THEN SLIDE BLISTER CARD UP." from all upper case to title case to improve readability. In addition, revise the statement (b) (4) to read similar to "Then slide blister card up completely and unfold the flap." for clarity.
4. As proposed, steps 1 and 2 on the inside panel have combined instructions for opening the blister card and removing a capsule. We recommend dividing the "Instructions" on the inside panel into two sections similar to "Instructions to open blister card" and "Instructions to remove capsules." The steps for opening the blister card and steps for removing the capsules should appear under the corresponding title.

   For the "Instructions to open blister card," revise the statement (b) (4) to read similar to "While holding tabs, slide blister card up completely and unfold the flap." for clarity.

   For the "Instructions to remove capsules," add the step of peeling the tab from either end to expose foil before the step of pushing the capsule through the backing. In addition, revise the statement (b) (4) to read "Remove dose by pushing END of capsule through the backing." for clarity.
5. On the inside flap where the capsules are removed from the blister, revise the title from "Instructions" to convey the intent of the instructions, similar to "Instructions to remove capsules."

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

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/s/

JULIE V NESHIEWAT
05/15/2013

IRENE Z CHAN
05/16/2013

SCOTT M DALLAS
05/16/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: January 15, 2013

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader
Pediatric and Maternal Health Staff

Lynne Yao, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP), CDER Office of Regulatory Policy, FDA Office of Chief Counsel

Drug: Trokendi XR (topiramate) extended-release capsules

NDA: 201635

Applicant: Supernus Pharmaceuticlas, Inc.

Subject: PMHS Response to Supernus Pharmaceutical Inc. October 31, 2012, Request for Comment Submission

INTRODUCTION AND BACKGROUND

Supernus requested a meeting with the Agency by letter dated July 24, 2012, to discuss the Tentative Approval action taken on June 25, 2012, for Trokendi XR (topiramate) extended-release capsules, NDA 201635. The Office of Chief Counsel (OCC), the Office of Regulatory Policy (ORP), the Division of Neurology Products (DNP), and the Pediatric and Maternal Health Staff (PMHS) met with the Applicant on October 3, 2012, to discuss the Tentative Approval action related to the Pediatric Exclusivity attached to Topamax[1] for the use of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, and the need for this information to appear in Trokendi XR labeling. The Applicant was told that they could submit for review, supported, alternative pediatric use language for the labeling of Trokendi XR and the Agency would determine if this information appropriately conveyed the pediatric safety information that is currently protected in Topamax labeling.[2]

On October 31, 2012, Supernus Pharmaceuticals Inc. submitted a Request for Comment (b) (4) pertaining to the Tentative Approval action taken on June 25, 2012, for Trokendi XR (topiramate) extended-release capsules, NDA 201635. Supernus submitted published literature to support the inclusion of alternative pediatric use information in the Trokendi labeling. OCC, ORP, DNP, and PMHS are reviewing the Applicant's October 31, 2012 Request for Comment Submission. Although PMHS's review summarizes some of the Agency's legal and policy discussions, PMHS's review will focus on the Applicant's clinical/scientific arguments for protected pediatric use labeling language alternatives. This review has also been prepared in consultation with DNP and other components of the Agency.

BACKGROUND

Best Pharmaceuticals for Children Act & Pediatric Research Equity Act

The goal of both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is to provide pediatric information in labeling to encourage the appropriate use of medications to treat pediatric patients. BPCA incentivizes Applicants to conduct pediatric studies by awarding an additional 6 months of exclusivity for voluntarily conducting FDA-requested studies under a Written Request (21 USC 355a). PREA requires certain applications to contain pediatric assessments under certain circumstances and authorized FDA to require holders of certain types of approved marketing applications to conduct pediatric studies under certain circumstances (21 USC 355c).

Labeling must be updated with the results of studies conducted under BPCA or PREA regardless of whether safety and effectiveness are established. In general, pediatric use information is incorporated solely in subsection 8.4 if safety and effectiveness are not

[1] Janssen Pharmaceuticals was awarded 3 years of Hatch-Waxman Exclusivity (expires December 22, 2012) for "information from pediatric studies added to the label" (M-54) , and an additional six months of Pediatric Exclusivity (expires June 22, 2013) under Best Pharmaceuticals for Children Act for meeting the terms of the Pediatric Written Request (PWR) (December 14, 2005)for Topamax® Tablets and Sprinkle Capsules.

[2] See October 3, 2012, meeting minutes.

established (with the exception of necessary contraindications and/or warnings and precautions) so as not to imply an indication. In contrast, pediatric use information is incorporated into all relevant sections of labeling when safety and effectiveness are established. FDA regulations include drug labeling provisions specific to the use of drugs in pediatric populations which are intended to maximize the availability of important pediatric safety information (e.g., 201.57(f)(9)).

Trokendi XR

On August 30, 2011, Supernus Pharmaceutical, Inc. submitted a 505(b)(2) New Drug Application for Trokendi XR (topiramate) extended-release capsules, NDA 201635. Supernus relies on the Agency's previous findings of safety and effectiveness for the listed drugs, Topamax tablets (NDA 20505) and capsules (NDA 20844). Supernus submitted only pharmacokinetic data to establish a bridge and bioequivalence from the approved immediate-release topiramate product to their extended-release topiramate product.

A Tentative Approval was issued on June 25, 2012, because FDA made the determination that the protected pediatric use information that appears in Topamax labeling related to the use of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months must remain in this Trokendi XR labeling for reasons of safe use Topamax Pediatric Exclusivity expires June 22, 2013).[3] Effectiveness was not demonstrated and an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality, were observed in the infant/toddler Topamax clinical study.[4]

Of note, FDA also had previously determined that this protected pediatric use information was necessary for the safe use of generic topiramate products and; therefore, this text was retained in generic topiramate labeling in accordance with the Best Pharmaceuticals for Children Act (BPCA).[5,6]

(b) (4)

The Pediatric Written Request was issued July 9, 2004 and amended December 14, 2005, requesting studies of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive.

[5] Section 505A(o) of the Best Pharmaceuticals for Children Act (BPCA) (section 505A(o) of the Food, Drug and Cosmetic Act) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. It provides that abbreviated new drug applications (ANDAs) may include protected warnings, precautions and contraindications and other information necessary to assure safe use regardless of whether such information is otherwise protected by exclusivity.

[6] See March 9, 2010, PMHS consult re: proposed labeling for generic topiramate tablets; See September 10, 2012, PMHS consult re: generic topiramate capsules and tablets. In September 2012, the Agency sent follow-up letters to applicants asking them to ensure the labeling was updated to include the information deemed necessary for safe use of the products.

Indications
Topamax is approved for the following indications:

- Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS)
- Migraine: Treatment for adults for prophylaxis of migraine headache

Supernus received a Tentative Approval for the following indications for Trokendi XR:

- initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures;
- adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures;
- adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Reviewer Comment: Topamax is approved for initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures; however, the 2 to 10 year old age group is protected by 3 years of Waxman-Hatch Exclusivity – New Patient Population (expires July 14, 2014). This study information fulfilled the Pediatric Research and Equity Act (PREA) postmarketing studies requirement issued June 29, 2005. No unique safety concerns were identified in these studies, and FDA determined that protected pediatric information regarding this population was not necessary for the safe use of *Trokendi.*

Topamax Infant/Toddler Labeling[7]
The infant/toddler protected pediatric use information was incorporated in the following sections/subsections of Topamax labeling:[8]

5 WARNINGS AND PRECAUTIONS
- 5.4 Metabolic Acidosis
- 5.8 Hyperammonemia and Encephalopathy
- 5.9 Kidney Stones
- 5.13 Monitoring: Laboratory tests

8 USE IN SPECIFIC POPULATIONS
- 8.4 Pediatric Use

[7] See Appendix A for side by side comparison of approved Topamax Pediatric Use Labeling and proposed Supernus Pediatric Use Labeling
[8] See current approved Topamax labeling, dated October 29, 2012

Reviewer Comment: The WARNINGS, AND PRECAUTIONS subsections 5.4, 5.8, 5.9, and 5.13, existed in Topamax labeling prior to the addition of the infant/toddler study results. These WARNINGS AND PRECAUTIONS subsections were updated and revised with the additional data from the infant/toddler study.

Applicant Arguments

Supernus believes that a Full Approval should be granted for Trokendi XR and requests the Agency to reconsider its Tentative Approval decision based on the following arguments:

(b) (4)

Supernus provided proposed (b) (4)

(b) (4)

PMHS SUMMARY RESPONSES

1. (b) (4) of label language for a 505(b)(2) New Drug Application.

   The Applicant states that their product is not intended for use in children under 6 years of age which they assert is clearly stated in Trokendi XR labeling. Furthermore, the Applicant states that FDA's labeling regulations permit the Agency to require statements that are related to uses not listed in the Indications and Usage section in labeling only in specific circumstances (i.e., if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard). (b) (4)

PMHS Response
Pediatric product development legislation (BPCA and PREA) was enacted because of the recognition that drugs approved for adults for indications that occurred in pediatric populations were being used in pediatric populations despite the lack of adequate labeling for those populations, with potentially dangerous results. BPCA and PREA together used a "carrot and stick" approach to address the lack of pediatric information in drug labeling and to ensure drugs for indications that occur in children would be appropriately labeled for use in children. Prior to the enactment of pediatric legislation, there was a paucity of drugs that contained pediatric labeling to adequately inform use of a drug in children and the majority of drugs used in children were used without appropriate safety, effectiveness or dosing information for pediatric age groups. Outpatient utilization data presented at the Pediatric Advisory Committee Meeting on September 23, 2011, reported 8900 Topamax prescriptions in patients 0 to 1 year of age between April 2007 and March 2011.[9] There is no infant/toddler age group indication for Topamax and the Topamax study conducted in this age group failed to demonstrated effectiveness, but demonstrated an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality. However, there are few anti-epileptic drugs approved in infants and toddlers and topiramate is used for seizure control when necessary in this age group. Because of the efficacy and safety concern with the use of topiramate in infants and toddlers, clinicians need access to the available benefit/risk information for informed prescribing decisions. Further, labeling regulations (e.g., 21 CFR 201.57(f)(9)) require labeling to include a description of hazards associated with use of a drug in a pediatric population for which the requirements for substantial evidence of effectiveness have not been met. (b) (4) .

2. The information that the Division requests (b) (4)

   The Applicant states that their extended-release topiramate product is not intended for use in infants and toddlers and that they have placed appropriate messages in labeling regarding the need to swallow the capsule whole and not open and sprinkle on food, or chew or crush. The Applicant also states that safety and efficacy were not established in the Topamax study conducted in pediatric patients ages 1 to 24 months; (b) (4)

PMHS Response
FDA, not the Applicant, makes the determination (b) (4) is necessary to ensure the safe use of both 505(j) and 505(b)(2) products. (b) (4) (b) (4)

[9] See Pediatric Safety Review - Topamax, Pediatric Advisory Committee Meeting, September 23, 2011

In addition, there is no evidence to suggest, despite labeled warnings, that the Trokendi XR capsule will not be opened. The capsule can be opened and is likely to be opened for use in a patient of any age who is unable to swallow capsules whole.

As previously noted, there are few anti-epileptic drugs approved for infants and toddlers. The fact that effectiveness with Topamax was not established in young patients; and an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality, were observed, make it is all the more compelling to include this information in all topiramate labeling. The assignment of safety effects in the absence of effectiveness is important to provide benefit/risk information for prescribing decisions in children. For this very reason, drug product labeling is required to be updated with the results of studies conducted under BPCA or PREA regardless of whether safety and effectiveness were established. (b) (4)

(b) (4)

PMHS Response

A 505(b)(2) drug product is not required to have labeling that is identical to the listed drug. Supernus submitted a 505(b)(2) application which relies on the Agency's findings of safety and efficacy for Topamax, and submitted only pharmacokinetic data to establish a bridge and bioequivalence from the approved immediate-release topiramate product to their extended-release topiramate product. In addition, the Applicant itself proposed identical labeling to Topamax for the sections of labeling that they relied on for previous findings of safety and efficacy, including the protected infant/toddler study information. (b) (4)

Regardless, FDA has determined that the information on the infant/toddler study is necessary for the safe use of Trokendi XR.

Reviewer Comment: Supernus did not include the Topamax adult migraine indication in Trokendi XR labeling, as the migraine indication remains under patent protection.

During the June 29, 2012, teleconference, FDA told the Applicant that section 505A(o) of the FD&C Act (BPCA) allows the retention of protected pediatric use information in 505j products when the protected pediatric use information is necessary for the safe use of the generic drug product. The Agency previously determined that the infant/toddler information is necessary for the safe use of topiramate generic products. There are no provisions allowing retention of protected but essential pediatric information for 505(b)(2) products. When FDA determines that protected pediatric use information must remain in a 505(b)(2) product's labeling for reasons of safe use, then the Applicant can receive only a Tentative Approval until the exclusivity expires.

4. (b) (4)

PMHS Response

The Applicant's contention that the public health is promoted with once daily topiramate versus twice daily topiramate because one daily dosing increases patient compliance is speculative. The Applicant did not study patient compliance of these different dosing regimens, or the effect of these different dosing regimens on seizure control. Furthermore, although not studied, missing a dose of a once daily topiramate product versus missing one dose of a twice-a-day immediate release topiramate product may have a worse adverse impact on seizure control.

The Applicant did not provided sufficient data to FDA to support their claim that a (b) (4) Furthermore, as previously stated, the information from the Topamax infant/toddler study should appear in all topiramate labeling for benefit/risk prescribing decisions when topiramate is considered as an option for use in young children with seizure disorders, as effectiveness was not established and safety concerns were observed. Therefore, PMHS disagrees with the Applicant's argument that the (b) (4)

Proposed Pediatric Use Labeling[10]

The Applicant proposed (b) (4) for Trokendi XR labeling in (b) (4) .

PMHS Response

A detailed description of the infant/toddler study appears in the Pediatric Use subsection of Topamax labeling, with important data from the study further described in various subsections of the Warnings and Precautions section of labeling. The Applicant's proposed (b) (4) For example, the Applicant's proposed (b) (4) Appendix A includes a side by side comparison of the Topamax labeling and Trokendi XR proposed labeling, and explains why the Trokendi proposed labeling is not adequate. The Trokendi XR pediatric use language (b) (4) .

CONCLUSIONS Supernus failed to provide an adequate justification to support the (b) (4) (b) (4) labeling; pediatric use information that is protected by Pediatric Exclusivity until June 22, 2013. FDA determined that this protected pediatric use information was necessary for the safe use of Trokendi XR. No topiramate product is approved in the infant/toddler age group. The Topamax study conducted in this vulnerable population failed to demonstrate efficacy, but an increased risk of known drug-related adverse reactions as well as unique safety concerns, including mortality, were observed. There are few anti-epileptic drugs approved in infants and toddlers and drugs approved for adults or older pediatric patients are likely to be used in this population. Clinicians require adequate risk/benefit information, when available in drug product labeling, for making prescribing decisions when considering use in an infant or toddler. The Applicant failed (b) (4) .

RECOMMENDATIONS

PMHS recommends that the Applicant be informed that they failed to provide an adequate justification to support (b) (4) In addition, the Applicant failed to (b) (4)

[10] See Appendix A for side by side comparison of approved Topamax Pediatric Use Labeling and proposed Supernus Pediatric Use Labeling


(b) (4)

APPENDIX A – Side-By-Side Pediatric Use Labeling

Protected Topamax Pediatric Use Labeling (Infant/Toddler Study)	Proposed Alternative Topiramate Extended-Release Capsules Pediatric Use Labeling	PMHS Comments
5.4 Metabolic Acidosis Although not approved for use in patients under 2 years of age with partial onset seizures, a controlled trial that examined this population revealed that topiramate produced a metabolic acidosis that is notably greater in magnitude than that observed in controlled trials in older children and adults The mean treatment difference (25 mg/kg/d topiramate-placebo) was -5.9 mEq/L for bicarbonate. The incidence of metabolic acidosis (defined by a serum bicarbonate < 20 mEq/L) was 0% for placebo, 30% for 5 mg/kg/d, 50% for 15 mg/kg/d, and 45% for 25 mg/kg/d [*see Pediatric Use (8.4)*]. Long-term, open-label treatment of infants/toddlers, with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in Z SCORES for length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal infants. Reductions in Z SCORES for length and weight were correlated to the degree of acidosis *[see Pediatric Use (8.4)]*. **5.8 Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use)** …and in very young pediatric patients (1-24 months) who were treated with adjunctive topiramate for partial onset epilepsy (8% for placebo, 10 % for 5 mg/kg/day, 0 % for 15 mg/kg/day, 9 % for 25 mg/kg/day). Topiramate is not approved as monotherapy for migraine	(b) (4)	The Applicant's proposed (b) (4) .

prophylaxis in adolescent patients or as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. Although topiramate is not indicated for use in infants/toddlers (1-24 months) VPA clearly produced a dose-related increased in the incidence of treatment-emergent hyperammonemia (above the upper limit of normal, 0% for placebo, 12% for 5 mg/kg/day, 7% for 15 mg/kg/day, 17% for 25 mg/kg/day) in an investigational program. Markedly increased, dose-related hyperammonemia (0% for placebo and 5 mg/kg/day, 7% for 15 mg/kg/day, 8 % for 25 mg/kg/day) also occurred in these infants/toddlers. Dose-related hyperammonemia was similarly observed in a long-term, extension trial in these very young, pediatric patients *[see Use in Specific Populations (8.4)]*. **5.9 Kidney Stones** During long-term (up to 1 year) topiramate treatment in an open-label extension study of 284 pediatric patients 1-24 months old with epilepsy, 7% developed kidney or bladder stones that were diagnosed clinically or by sonogram. Topiramate is not approved for pediatric patients less than 2 years old *[see Pediatric Use (8.4)]*. **5.13 Monitoring: Laboratory Tests** Changes in several clinical laboratory values (increased creatinine, BUN, alkaline phosphatase, total protein, total eosinophil count and decreased potassium) have been observed in a clinical investigational program in very young (<2 years) pediatric patients who were treated with adjunctive topiramate for partial onset seizures [*see Pediatric Use (8.4)*].	(b) (4) **5.9 Kidney Stones** No alternate language proposed by Applicant. (b) (4)	(b) (4) (b) (4)

(b) (4)

(b) (4)

(b) (4)

8.4 Pediatric Use

Adjunctive Treatment for Partial Onset Epilepsy in Infants and Toddlers (1 to 24 months)

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. In a single randomized, double-blind, placebo-controlled investigational study, the efficacy, safety, and tolerability of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent antiepileptic drug therapy in infants 1 to 24 months of age with refractory partial onset seizures were assessed. After 20 days of double-blind treatment, topiramate (at fixed doses of 5, 15, and 25 mg/kg/day) did not demonstrate efficacy compared with placebo in controlling seizures.

In general, the adverse reaction profile in this

population was similar to that of older pediatric patients, although results from the above controlled study and an open-label, long-term extension study in these infants/toddlers (1 to 24 months old) suggested some adverse reactions/toxicities (not previously observed in older pediatric patients and adults; i.e., growth/length retardation, certain clinical laboratory abnormalities, and other adverse reactions/toxicities that occurred with a greater frequency and/or greater severity than had been recognized previously from studies in older pediatric patients or adults for various indications.

These very young pediatric patients appeared to experience an increased risk for infections (any topiramate dose 12%, placebo 0%) and of respiratory disorders (any topiramate dose 40%, placebo 16%). The following adverse reactions were observed in at least 3% of patients on topiramate and were 3% to 7% more frequent than in patients on placebo: viral infection, bronchitis, pharyngitis, rhinitis, otitis media, upper respiratory infection, cough, and bronchospasm. A generally similar profile was observed in older children *[see Adverse Reactions (6)]*.

Topiramate resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5%, placebo 0%), BUN (any topiramate dose 3%, placebo 0%), and protein (any topiramate dose 34%, placebo 6%), and an increased incidence of decreased potassium (any topiramate dose 7%, placebo 0%). This increased frequency of abnormal values was not dose-related. Creatinine was the only analyte showing noteworthy increased incidence (topiramate 25 mg/kg/day 5%, placebo 0%) of a markedly abnormal increase [see Warnings

(b) (4)

and precautions (5.15)]. The significance of these findings is uncertain. Topiramate treatment also produced a dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10% for 5 mg/kg/day, 9% for 15 mg/kg/day, 14% for 25 mg/kg/day, and 11% for any topiramate dose *[see Warnings and Precautions (5.15)]*. There was a mean dose-related increase in alkaline phosphatase. The significance of these findings is uncertain. Topiramate produced a dose-related increased incidence of treatment-emergent hyperammonemia *[see Warnings and Precautions (5.9)]*. Treatment with topiramate for up to 1 year was associated with reductions in Z SCORES for length, weight, and head circumference *[see Warnings and Precautions (5.3) and Adverse Reactions (6)]*. In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment-related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) *[see Warnings and Precautions (5.5)]*.	(b) (4)	

In this open-label, uncontrolled study, the mortality was 37 deaths/1000 patient years. It is not possible to know whether this mortality rate is related to topiramate treatment, because the background mortality rate for a similar, significantly refractory, young pediatric population (1-24 months) with partial epilepsy is not known.		

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/s/

JEANINE A BEST
01/15/2013

HARI C SACHS
01/15/2013
I agree with these recommendations.

LYNNE P YAO
01/15/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Pediatric and Maternal Health Staff Memorandum

Date: June 12, 2012

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Lisa Mathis, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP)

Drug: Trokendi (topiramate) extended-release capsules

NDA: 201635

Sponsor: Supernus Pharmaceuticlas, Inc.

Subject: 505(b)(2) Application and protected pediatric information (Pediatric and Waxman-Hatch Exclusivity)

INTRODUCTION AND BACKGROUND

On August 30, 2011, Supernus Pharmaceutical, Inc. submitted a 505(b)(2) New Drug Application for Trokendi (topiramate) extended-release capsules, NDA 201635. The Reference Listed Drug (RLD) is Topamax (topiramate) tablets for oral use, NDA 20505. Supernus is relying on findings of safety and efficacy from NDA 20505 and has submitted only pharmacokinetic data to establish a bridge and bioequivalence from the approved immediate-release topiramate product to their extended-release topiramate product.

Topamax is approved for the following indications:

- *Monotherapy epilepsy: Initial monotherapy in patients ≥ 2 years of age with partial onset or primary generalized tonic-clonic seizures*
- *Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS)*
- *Migraine: Treatment for adults for prophylaxis of migraine headache*

Supernus is seeking approval for the following indications for Trokendi:

- *Monotherapy epilepsy: Initial monotherapy in patients* (b) (4) *with partial onset or primary generalized tonic-clonic seizures.*
- *Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients* (b) (4) *with partial onset seizures or primary generalized tonic-clonic seizures, and in patients* (b) (4) *with seizures associated with Lennox-Gastaut syndrome (LGS).*

Janssen Pharmaceuticals was awarded 3 years of Waxman-Hatch Exclusivity (expires December 22, 2012) for revisions to Topamax labeling based on data submitted in response to a Pediatric Written Request (December 14, 2005), and an additional six months of Pediatric Exclusivity (expires June 22, 2013) under BPCA for meeting the terms of the PWR for Topamax® Tablets and Sprinkle Capsules, and the company was awarded three-years of Waxman-Hatch (W-H) Exclusivity. The Pediatric Written Request was issued July 9, 2004 and amended December 14, 2005, requesting studies of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months, inclusive. Efficacy was not demonstrated and an increased risk of known drug-related adverse reactions as well as unique safety concerns, including death, were observed in pediatric studies with Topamax for use as adjunctive therapy in the treatment of partial seizures in patients 1 month to 24 months of age. The study data was incorporated in the Pediatric Use subsection of Topamax labeling and retained in generic topiramate labeling for reasons of safe use, as allowed by the Best Pharmaceuticals for Children Act (BPCA).[1] BPCA does not have carve-out or

[1] The Best Pharmaceuticals for Children Act (BPCA) (section 505A of the Food, Drug and Cosmetic Act) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling.

retention provisions for protected pediatric information in 505(b)(2) products. both PMHS and DNP agreed that this protected pediatric use information must remain in Trokendi labeling for reasons of safe use; therefore, Trokendi cannot receive a full approval until expiration of the Pediatric Exclusivity on June 22, 2013. A Tentative Approval may be issued in the interim.

Janssen Pharmaceuticals was awarded 3 years of Waxman-Hatch Exclusivity – New Patient Population (expires July 14, 2014) for revisions to Topamax labeling to include pediatric use information for initial monotherapy in patients 2 to 10 years of age with partial onset or primary generalized tonic-clonic seizures. This study information fulfilled the Pediatric Research and Equity Act (PREA) postmarketing commitment issued June 29, 2005. The data submitted for the approval of monotherapy in this age group was a re-analysis of previous submitted data in or determine appropriate monotherappy dosing in pediatric patients ages 2 to 10 years of age. Generic topiramate labeling does not contain this protected pediatric use information as generic topiramate was approved prior to the monotherapy approval in pediatric patients 2 to 10 years of age. No unique safety concerns were noted in the previously submitted efficacy trials for initial monotherapy in patients 2 to 10 years of age with partial onset or primary generalized tonic-clonic seizures. This protected pediatric safety information may be safely omitted from Trokendi labeling.

PMHS RECOMMENDATIONS

1. The protected pediatric use information related to the use of Topamax as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month (corrected age of at least 44 weeks gestational age) to 24 months must remain in Trokendi labeling for reasons of safe use; therefore, Trokendi cannot receive a full approval until expiration of the Pediatric Exclusivity on June 22, 2013.

2. The protected pediatric use information related to initial monotherapy in pediatric patients 2 to 10 years of age with partial onset or primary generalized tonic-clonic seizures may be safely omitted from Trokendi labeling; therefore the approval of Trokendi is not impacted by the Waxman-Hatch New Patient Population Exclusivity that expires on July 14, 2014.

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/s/

JEANINE A BEST
06/12/2012

LISA L MATHIS
06/14/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**Trokendi XR (topiramate) extended-release capsules for oral use**
Applicant	Supernus Pharmaceuticals
Application/Supplement Number	NDA 201,635/S1
Type of Application	Original NDA – 505(b)(2)
Indication(s)	1. Partial Onset Seizure and Primary Generalized Tonic-Clonic Seizures 2. Lennox-Gastaut Syndrome
Established Pharmacologic Class[1]	antiepileptic drug
Office/Division	ODEI/DNP
Division Project Manager	Jackie Ware
Receipt Date	September 9, 2011
PDUFA Goal Date	July 9, 2012
SEALD Review Date	June 13, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

NO 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *There are several boxes around the HL. The Patient Counseling Information statement and Revision date are in a separate box. There should be no box around the HL. The Patient Counseling Information statement should be below the Use in Special Populations section.*

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *DNP will likely grant a waiver for the 1/2 page length requirements for HL.*

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Applicant should extend the horizontal line for all the headings in the HL*

NO 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Add a reference (2.8) after the statement "Swallow capsule whoe and intact. Do not sprinkle on food, chew, or crush."*

NO 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information (SRPI) Revised

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *All headings are in correct order except the Patient Counseling Information statement and the Revision Date are separated (in a different box). The Patient Counseling Information statement and the Revision Date should be beneath the Use in Special Populations heading. Also, the applicant's name "Supernaus Pharmaceuticals, Inc." should be removed beneath the product title.*

YES 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *Trademark symbols should be removed.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Applicant must insert U.S. phone number.*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Add a colon.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment: *There should not be a box around the TOC and there should not be columns or rows.*

NO 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment: *Remove the"Highlights of Prescribing Information" after the Full Prescribing Information:Contents."*

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *1. Correct spelling in Section 5.1 title; 2. Correct title in Section 6.1 title; 3. Sections 12.4 and 12.5 are reserved for Microbiology and Pharmacogenomics. The information under these sections should be included in Section 12.3; 4. Correct spelling of Section 14.1.*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment: *Recommend that there is less space between the number of the section and the title of the section.*

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment: *Recommend that the subsection and section headings not be italicized and be 12-point fon (not 14-point font).*

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Sections 12.4 and 12.5 are reserved. The verbiage about Special Populations and Drug Interaction Studies should be included under Section 12.3.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *Multiple incorrect cross-references.*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Place at beginning of Section 17; also do not use bold type.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC R BRODSKY
06/13/2012

LAURIE B BURKE
06/14/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 21, 2012

TO: Russell G. Katz, M.D.
Director, Division of Neuropharmacology Products

FROM: Michael F. Skelly, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIRs Covering NDA 201-635, Topiramate ER Capsules, Sponsored by Supernus Pharmaceuticals, Inc.

At the request of the Division of Neuropharmacology Products (DNP) and the Office of Clinical Pharmacology, the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following studies:

Study 539P103: "A phase-I, single-center, multi-dose, randomized, single-blind, two-treatment crossover study to determine the pharmacokinetic profile of SPN-538 (topiramate Controlled-Release) Capsules relative to Topamax® tablets in healthy adult volunteers"

Clinical Site: Quintiles Phase I Unit
Overland Park, KS

Study 538P106-200: "A single-center, single-dose, open-label, randomized, two-treatment, two-period, two-sequence, crossover relative bioavailability study of Topiramate Extended-Release (TPM-XR) 200 mg capsules in healthy adult volunteers under fasting conditions"

Clinical Site: Dedicated Phase I, Inc. (now closed)
Phoenix, AZ

Study 538P106: "A single-center, single-dose, open-label, randomized, two-period, two-treatment, two-sequence crossover relative bioavailability study of Topiramate Controlled-Release (TPM-CR) 100 mg capsules in healthy adult volunteers under fasting conditions"

and

Study 538P106-50: "A single-center, single-dose, open-label, randomized, two-treatment, two-period, two-sequence, crossover relative bioavailability study of Topiramate Extended-Release (TPM-XR) 50 mg capsules in healthy adult volunteers under fasting conditions"

Clinical Site: PAREXEL International
Baltimore, MD

Analytical Site: Supernus Pharmaceuticals, Inc.
Rockville, MD

The inspections of the clinical portions were conducted at Quintiles, Overland Park, KS (study 538P103; 3/6-3/9/12); Bell Road Business Center, Phoenix, AZ (study 538P106-200; 3/12-3/16/12); and PAREXEL International, Baltimore, MD (studies 538P106 and 538P106-50; 1/4-1/10/12). The inspection of the analytical portions was conducted at Supernus Pharmaceuticals, Rockville, MD (four studies; 2/6-2/9/12).

Following the inspections, Form FDA-483 was issued only at Bell Road Business Center, to the former proprietor of Dedicated Phase I. The observation and our evaluation follow.

1) **The final protocol dated 14 Sep 2010 Page 20 of 39 states that serial blood samples (PK) will be taken from the dosed (one dose on day 1 and one dose on day 19) subjects at the following time intervals expressed in hours: 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 48, 72 and 96. The 2 hour blood sample was not taken on day 19 for the subject 110.**

The study report (p. 35) revealed that sampling times were not recorded at a single sampling time for three subjects, including #110 (P2-2h), #120 (P2-2h), and #132 (P2-36h). The actual time does not appear in Listing 16.2.6.1 of the final report for these subjects, but plasma samples for the scheduled times resulted in measured concentrations of topiramate. The scheduled times are well-separated from $t_{max.}$ The measured concentrations and undocumented times are unlikely to influence

C_{max}, AUC, or AUC_{∞} parameters and bioequivalence assessments, whether or not the observations are used in calculations.

Conclusions:

Following the inspections, DBGC recommends the following:

- The OCP reviewer should judge the impact of the three undocumented pharmacokinetic sampling times.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly , Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classifications:

NAI – Quintiles Phase 1 Unit, Overland Park, KS
FEI: 3006737338

VAI – Dedicated Phase 1, Phoenix, AZ
FEI: 3009443882

NAI – PAREXEL International, Baltimore, MD
FEI: 3005445577

NAI – Supernus Pharmaceuticals, Rockville, MD
FEI: 3005209462

cc:
OSI/Ball/Moreno
OSI/DBGC/Taylor/Haidar/Skelly/Dejernett
OND/DNP/Ware
OCP/DCPI/Wu/Men
HFR-SW3515/Mueller
HFR-PA2530/Kapsala
HFR-CE250/McFiren
HFR-CE250/Harris
CDER DSI PM TRACK
Draft: MFS 3/20/2012
Edit: SHH 3/20/2012
DSI: BE6278; O:\Bioequiv\EIRCover\201635.sup.top.doc
FACTS: 1369811

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL F SKELLY
03/21/2012

SAM H HAIDAR
03/23/2012

WILLIAM H TAYLOR
03/23/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # **201635** BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Trokendi (Alternate: (b) (4)) Established/Proper Name: Topiramate Dosage Form: Extended-Release Capsules Strengths: 25 mg, 50 mg, 100 mg and 200 mg		
Applicant: Supernus Pharmaceuticals, Inc Agent for Applicant (if applicable):		
Date of Application: August 30, 2011 Date of Receipt: September 9, 2011 Date clock started after UN:		
PDUFA Goal Date: July 9, 2012	Action Goal Date (if different):	
Filing Date: November 8, 2011	Date of Filing Meeting: October 26, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): • Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients greater than or equal to (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS). • Initial monotherapy in patients greater than or equal to (b) (4) with partial onset or primary generalized tonic-clonic seizures.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☒
Part 3 Combination Product? NO ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND **101670**	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.			✓	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			✓	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	✓			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 020505	Topamax tablet	M-54	December 22, 2012
NDA 020505	Topamax tablet	PED	June 22, 2013

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*		✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			✓	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			✓	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			eCTD backbone
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			✓	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	✓			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			✓	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			✓	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			PMHS consult
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			✓	(b) (4)
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			✓	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		✓		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	✓			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		✓		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	✓			
Is the PI submitted in PLR format?[4]	✓			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			Request applicant to resubmit draft carton & container labels
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	✓			Biopharm 9/20/11 OMPQ 9/21/11 DSI Bioequiv. 11/9/11
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** Oct 15, 2009 (DNP) & Apr 25, 2010 (CMC only) ***If yes, distribute minutes before filing meeting***	✓			

✓

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Sept 2, 2010 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		✓		

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 26, 2011

NDA #: 201635

PROPRIETARY NAME: Trokendi (Alternate: (b) (4))

ESTABLISHED/PROPER NAME: Topiramate

DOSAGE FORM/STRENGTH: Extended-Release Capsule

APPLICANT: Supernus Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients greater than or equal to (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS).
- Initial monotherapy in patients greater than or equal to (b) (4) with partial onset or primary generalized tonic-clonic seizures

BACKGROUND:
Supernus Pharmaceuticals has developed an extended release capsule formulation of topiramate. This NDA is filed under Section 505(b)(2), identifying NDA 020505 marketing Topamax as the reference listed drug. The current submission is a resubmission after Refuse to File on March 14, 2011. The firm proposes to market 4 strengths: 25 mg, 50 mg, 100 mg and 200 mg.

Topiramate was originally developed by Ortho McNeil/Janssen Pharmaceuticals (Ortho) for treatment of epilepsy. The innovator product, Topamax® (topiramate) Tablets (the RDL) was approved under NDA 020505 in 1996.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jacqueline Ware Fannie Choy	Y Y
	CPMS/TL:	Robbin Nighswander	N
Cross-Discipline Team Leader (CDTL)	Angela Men		Y
Clinical	Reviewer:	Martin Rusinowitz	Y
	TL:	Norman Hershkowitz	Y

Clinical Pharmacology	Reviewer:	Ta-chen Wu	N
	TL:	Angela Men	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	J Edward Fisher	Y
	TL:	Lois Freed	N
Product Quality (CMC)	Reviewer:	Thomas Wong	Y
	TL:	Martha Heimann	Y
Biopharmaceutics	Reviewer:	Selen Arzu	N
	TL:	Angelica Dorantes	N
Facility Review/Inspection	Reviewer:	Shawn Gould	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE	RPM:	Laurie Kelley	Y
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Michael Skelly	Y
	TL:	Sam Haidar	N
Other reviewers	Eric Brodsky, SEALD Labeling		N
Other attendees	Russell Katz, Division Director Colleen Locicero, ADRA Nicole Bradley, RPM		Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO

• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Approval is relied on PK study	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: EA has been submitted in original filing and can be applied to re-submission (per CMC).	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division Director

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Filing goal date (day 60): **Nov 8, 2011**
74-day Letter goal date: **Nov 22, 2011**
PDUFA Action goal date: **July 9, 2012**

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing.

	Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Fannie Choy

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
06/06/2012

JACQUELINE H WARE
06/08/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 23, 2012

To: Jacqueline Ware, Senior Regulatory Project Manager
Division of Neurology Products (DNP)

From: Quynh-Van Tran, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Sharon Watson, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Group Leader (Acting), DCDP/OPDP
Andy Haffer, Division Director (Acting), DCDP/OPDP
Mathilda Fienkeng, Team Leader (Acting), DCDP/OPDP

Subject: NDA 201635
Trokendi (topiramate) Extended Release capsules

OPDP Labeling Consult Request

In response to DNP's November 3, 2011, consult request, OPDP has reviewed the draft package insert (PI) and Medication Guide for Trokendi and offers the following comments.

OPDP's comments on the PI are based on version that Jacqueline Ware sent via email on May 7, 2012. OPDP used the Division's tracked changes version of the Medication Guide from the DNP e-room titled "TROKENDI XR N201635 medication-guide WORKING VERSION.doc," accessed at 0745 AM on May 23, 2012, as the base document for review. OPDP's comments on the PI and Medication Guide are provided directly on the document attached below.

If you have any questions regarding the PI, please contact Quynh-Van Tran at 301.796.0185. If you have any questions regarding the Medication Guide, please contact Sharon Watson at 301.796.3991 or sharon.watson@fda.hhs.gov.

55 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON M WATSON
05/23/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	May 17, 2012
Reviewer:	Julie Neshiewat, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Trokendi XR (Topiramate) Extended-release Capsules 25 mg, 50 mg, 100 mg, 200 mg
Application Type/Number:	NDA 201635
Applicant:	Supernus Pharmaceuticals
OSE RCM #:	2011-3357

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container labels, blister card labeling, Medication Guide, and package insert labeling for Trokendi XR (Topiramate) Extended-release Capsules (NDA 201635) for areas of vulnerability that could lead to medication errors. If approved, this product will be the first extended-release topiramate product on the market.

1.1 REGULATORY HISTORY

This is a 505(b)(2) application. The reference listed drugs are Topamax Tablets (NDA 020505) and Topamax Sprinkle Capsules (NDA 020844). The Applicant submitted the NDA application on January 14, 2011. A Refuse to File (RTF) letter was sent to the Applicant on March 14, 2011 due to chemistry, manufacturing, and controls issues. The Applicant re-submitted the NDA application on August 30, 2011.

On March 22, 2012, the Applicant mailed samples of the blister pack utilized for (b) (4) testing activities that contained no artwork. Then, on April 19, 2012, the Applicant mailed sample (b) (4) 30-count blister packs for each product strength that contained artwork. After reviewing the samples of both blister pack versions we noted there were differences in the materials used for the packaging. We also noted that with both versions, the capsules were difficult to remove from the blister packs and in some instances the capsules were crushed as we attempted to remove them. On May 2, 2012, the Division of Medication Error Prevention (DMEPA) and the the Division of Neurology Products (DNP) held a teleconference with the Applicant to discuss our concerns with the blister packaging and to request that the Applicant conduct a usability study to verify that patients can access the medication. Since we identified concerns with the blister packaging and there is no evidence to support the usability of the blister packaging, DNP indicated that an action would only be taken on the bottle configurations. The Applicant acknowledged our concerns and will be taking steps to address the issues.

The proprietary name for this product is Trokendi XR, which we evaluated under separate cover (OSE Review # 2012-183).

1.2 PRODUCT INFORMATION

The following product information is provided in the September 9, 2011 insert labeling submission.

- Active Ingredient: Topiramate
- Indication of Use: Monotherapy for patients (b) (4) with partial onset or primary generalized tonic-clonic seizures; Adjunctive therapy for patients (b) (4) with partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome
- Route of Administration: Oral
- Dosage Form: Extended-release Capsules
- Strength: 25 mg, 50 mg, 100 mg, 200 mg
- Dose and Frequency: 25 mg (based on a range of 1 mg/kg/day to 3 mg/kg/day in patients (b) (4) for adjunctive therapy) to 50 mg daily titrated weekly by 25 mg

(based on a range of 1 mg/kg/day to 3 mg/kg/day in patients [redacted] (b) (4) for adjunctive therapy) to 50 mg increments to an effective dose not to exceed 400 mg daily (based on a range of 5 mg/kg/day to 9 mg/kg/day in patients [redacted] (b) (4) for adjunctive therapy)

- How Supplied: 100-count retail bottle, 30-count retail blister cards, [redacted] (b) (4)
- Storage: Store at 15° C to 30° C (59° F to 86° F). Protect from moisture.
- Container and Closure Systems: [redacted] (b) (4) blister cards with [redacted] (b) (4) 120 cc wide-mouth white high-density polyethylene square bottles with 38 mm white [redacted] (b) (4) closure [redacted] (b) (4)

2 METHODS AND MATERIALS REVIEWED

This product will be the first marketed extended-release topiramate, if approved. However, there already exists the currently marketed capsule formulation of immediate-release topiramate, Topamax Sprinkle Capsules, which can be opened and sprinkled on soft food. Therefore, DMEPA searched the FDA AERS database for Topamax (Topiramate) medication error reports in pediatric patients since we were interested in determining dosing and administration errors in the pediatric population with the existing capsules. We also reviewed the Topiramate Extended-release Capsules container labels, blister card labeling, Medication Guide, and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy

Date	February 29, 2012
Drug Names	Topiramat% (active ingredient) Topama% (trade name) Topiramat%, Topama% (verbatim terms)
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (PT)
Limitations	Age range: 0 years to 12 years

The AERS database search identified 92 reports. Each report was reviewed for relevancy and duplication. Our focus was identifying medication errors related to dosage and administration of Topamax. After individual review, 64 reports were not included in the final analysis for the following reasons:

Product quality issue with generic substitution (n = 18)

Duplicate reports (n = 16)

Accidental exposure or accidental intake by a child, cause unknown (n = 10)

Exposure during pregnancy or lactation for which there is already adequate labeling (n = 6)

Wrong patient: prescribed in an age group not indicated (n = 5)

Medication errors and product quality issues with drugs other than Topiramate (n = 3)

Wrong drug (n = 3)

Dose omission (n = 2)

Wrong dosage form: administered tablets instead of sprinkle capsules, cause unknown (n = 1)

2.2 LABELS AND LABELING

Using the principals of Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 3, 2012 (Appendix B)
- Blister Card Labeling submitted February 3, 2012 (Appendix C and D)
- Medication Guide and Insert Labeling submitted September 9, 2011 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Topiramate Extended-release Capsule's labels and labeling.

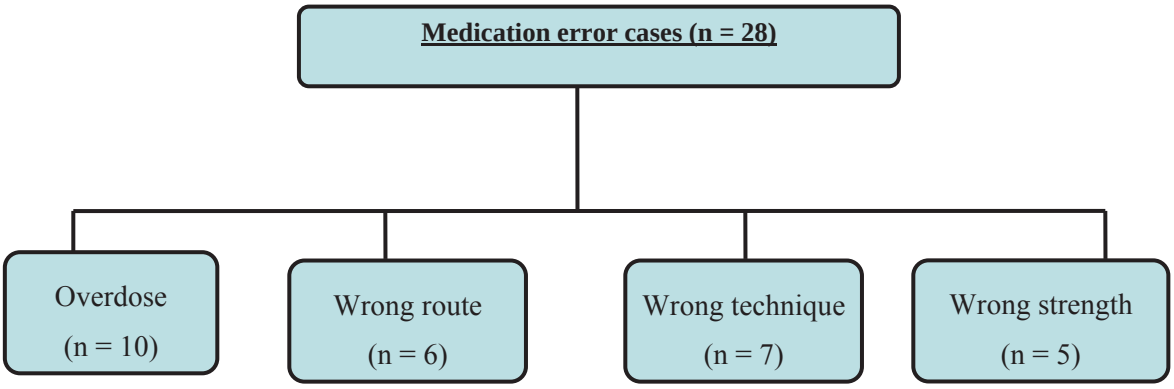
3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, twenty eight Topamax medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix E provides listings of all relevant ISR numbers for the cases summarized in this review. Appendix F provides listings of ISR numbers for the cases that were excluded.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

Figure 1: Topamax medication errors (n = 28) categorized by type of error



3.1.1 Wrong dose (n = 10)

One case described a wrong dose prescribing error, but no further details regarding cause and outcome were reported. The remaining nine cases described an overdose or suspected overdose. Most cases did not report a cause, but in four cases, contributing factors were noted as a heat spell or dehydration, impaired liver function, or rapid titration. Outcomes of these wrong dose errors included hospitalization, hallucinations, seizures, and anger outbursts. There is insufficient data to provide dosage recommendations in hepatic dysfunction for the proposed product, and the proposed insert labeling states that clearance of topiramate may be decreased in these patients. The proposed insert labeling has clear instructions for initiating and titrating topiramate extended-release capsules in the pediatric population.

3.1.2 Wrong route of administration (n = 6)

Five of the six cases describe topiramate given via nasogastric route with unknown causes or outcomes. The sixth case describes multiple drugs mixed into a syringe and given intravenously instead of via nasogastric route, but the cause was not noted. The patient experienced hypotension and cyanosis. It is unclear which formulation of topiramate was used in these wrong route cases. The product under review is a capsule that should not be opened. The proposed insert labeling indicates that the capsules should be swallowed whole and intact, and therefore cannot be given via nasogastric route. A similar statement on the proposed container labels and blister card labeling may help minimize the risk of wrong route of administration errors.

3.1.3 Wrong technique (n = 7)

These wrong technique cases describe crushing and splitting of tablets, compounding a solution from tablets, and sprinkling capsule contents onto melted chocolate and then freezing the chocolate. In two of the seven cases, the patient was prescribed to split the tablet. Outcomes included seizures, weakness, delayed response, and lack of efficacy. Four of the seven cases occurred in a patient less than 2 years of age, which is considered off

labeled use. The labeling of the marketed immediate-release topiramate states not to split the tablets due to the bitter taste. The proposed insert labeling indicates that the capsules should be swallowed whole and intact. A similar statement on the proposed container labels and blister card labeling may help to decrease wrong technique errors.

3.1.4 Wrong strength (n = 5)

Four of the wrong strength cases relate to a dispensing error and the fifth case relates to a transcribing error. One dispensing error case speculates that the pharmacist grabbed the wrong bottle since the different strengths of the product are beside each other on the shelf. Another dispensing error case, in which 15 mg and 25 mg sprinkle capsules were dispensed in the same pharmacy vial, states that both capsules look similar with a clear top and a white bottom. The cause for the other cases is unknown. Three of the five cases led to hospitalization, one error was caught before administration, and the other outcome is unknown. Two of the five cases occurred in a patient less than 2 years of age, which is considered off labeled use. The strengths of the proposed capsules, container labels, and blister card labeling are adequately differentiated by color.

3.2 Integrated Summary of Medication Error Risk Assessment

We considered the information obtained from the AERS cases when conducting our risk assessment of the labels and labeling. Our review identified the following deficiencies in the labels and labeling:

A. Packaging design of blister card labeling:

1. 30-count: The format for the blister card labeling is confusing. The maximum recommended dose for the proposed product is 400 mg, but the highest strength is 200 mg. In the case that a patient is prescribed 400 mg daily, two 30-count blister cards of 200 mg would need to be dispensed to the patient for a one-month supply. Morever, the 30-count packaging configuration may be confusing for a patient taking 400 mg daily, (b) (4) The rationale for marketing a 30-count blister card, when a 100-count bottle intends to be marketed in unclear. To obtain clarity on these issues, an information request was sent to the Applicant. The Applicant responded to the information request in a cover letter that we received on March 28, 2012. The Applicant proposes (b) (4) to prevent confusion. The Applicant also stated that the rationale for marketing a 30-count blister pack was mainly to allow a one-month supply to be dispensed at a time, which has stocking, time, and labor-saving costs benefits. Although the proposal (b) (4) may minimize confusion, the layout of the capsules in the blister card is still problematic. As currently presented, (b) (4) This atypical presentation may confuse the patient and the incorrect number of capsules may be accidentally administered. The Applicant did not provide human factors data to support this design of the blister pack. The blister card

labeling for the 30-count needs to be redesigned. The rationale for marketing the 30-count blister pack is reasonable.

2. (b) (4)

3. The (b) (4) 30-count blister cards submitted on April 19, 2012 have two major issues. The first problem is that after pushing through the black half-circle that states "Push," it is difficult to peel the tab to expose the foil on the back of the blister. A majority of the cardboard is left intact and the medication cannot be pushed through the foil. The second problem is that even after multiple attempts in peeling the cardboard tab off, it is difficult to push the capsule through the foil without crushing it. When the capsule is crushed, the contents inside the capsule can come out of the capsule. Given these problems, we have concerns that there are usability issues with the blister card packaging and that patients will have difficulty in accessing the medication.

B. Container Labels, Blister Card Labeling: 30-count retail, (b) (4)

1. The established name lacks prominence commensurate with the proprietary name.
2. Statements regarding once daily administration and swallowing capsules whole and intact are needed on the labels and labeling. Since the marketed Topiramate Immediate-release Tablets and Capsules can be administered once or twice daily, it is important to emphasize that this extended-release product is only administered once daily. Additionally, since the marketed Topamax Sprinkle Capsules can be opened and sprinkled on food, it is important to emphasize that this extended-release product must be swallowed whole and intact.
3. The graphic located above the proprietary name is overly prominent and situated too close to the proprietary name.
4. The blue wavy lined background composing the trade dress for this product may increase the risk for wrong strength selection errors during dispensing.
5. A statement instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed per 21 CFR 208.24 is missing.
6. The Supernus Pharmaceuticals logo is too prominent.

C. Blister Card Labeling: 30-count retail

1. The presentation of strength and dose with units does not appear within the same line of text on Panels A, B, D, and E, which decreases readability.
2. It is unclear if the presented strength is the total contents of the blister card or the total content per capsule.
3. The proprietary name and active ingredient information needs to appear on all panels that contain drug. If the panels are separated, there should be sufficient information on the blister cards to determine the proprietary name, active ingredient, and strength of the product.
4. A designated space for the pharmacy prescription label is absent.
5. A statement declaring the presence of FD&C Yellow No. 6 on the blister card labeling for the 50 mg, 100 mg, and 200 mg capsules is needed per 21 CFR 201.20(c).

D. (b) (4)

E. Medication Guide

1. Negative warnings, such as "Tradename may not be sprinkled on food...," should be prefaced by an affirmative warning to prevent misinterpretation of the information.
2. A statement that the product is administered once daily is needed.

F. Insert Labeling

1. Negative warnings, such as "Do not sprinkle on food...," should be prefaced by an affirmative warning to prevent misinterpretation of the information.

2. Error-prone abbreviations, [redacted] and dangerous symbols, [redacted] are utilized in the insert labeling that can be misinterpreted.[2]
3. Numbers without their corresponding units of measure are found in the insert labeling.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling are unacceptable as they lack a statement regarding once daily administration, lack a statement instructing the authorized dispenser to provide a Medication Guide to each patient, and lack the necessary information on all panels of the blister cards that contain drug. Moreover, the design of the blister card labeling is confusing and can lead to medication errors.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Packaging design of blister card labeling

The removal of [redacted] on the blister cards proposed by the Applicant will need to be implemented for the 30-count retail [redacted] blister cards.

Additionally, the design of the blister cards is confusing [redacted]. With this atypical presentation and grouping of capsules, the patient may infer that [redacted]. The blister cards should be redesigned with a packaging configuration that presents the medication in a linear manner and does not infer varying doses.

Moreover, it is difficult to access the medication through the blister card labeling. A majority of the cardboard is left intact and the medication cannot be pushed through the foil. Additionally, even after multiple attempts in peeling the cardboard tab off, it is difficult to push the capsule through the foil without crushing it. When the capsule is crushed, the contents inside the capsule can come out of the capsule. Given these problems with the proposed blister card labeling, a usability study to verify that patients can access the medication is needed.

B. Container Labels, Blister Card Labeling: 30-count retail, [redacted]

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

[2] Institute for Safe Medication Practices (ISMP). ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010.

2. To help distinguish this extended-release product from the marketed immediate-release topiramate products, add a descriptor indicating that the product should be dosed "Once Daily" and administration instructions to "**Swallow whole and intact.** Do not open, crush, chew, or sprinkle capsule contents on food." These statements should appear on the principle display panel.
3. Remove the circular graphic that appears above "XR." This graphic detracts from the proprietary name, active ingredient, and strength statement.
4. Remove the blue background found on the bottom half portion of the principal display panel, since it makes the four strengths appear similar to one another and increases the risk that the wrong strength is dispensed to patients.
5. Revise the presentation of "EXTENDED-RELEASE" from all upper case to title case "Extended-release" to improve readability.
6. Add a statement to the principal display panel instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed per 21 CFR 208.24.
7. Decrease the size of the Supernus Pharmaceuticals logo since it detracts from the proprietary name, active ingredient, and strength.
8. In order to accommodate the "Once Daily" and "**Swallow whole and intact.** Do not open, crush, chew, or sprinkle capsule contents on food," relocate the "Rx only" statement to the bottom right corner.

C. Blister Card Labeling: 30-count retail

1. In some instances, the strength with units does not appear within the same line of text. Revise the strength presentation to ensure the units appear next to the number to improve readability.
2. Revise the strength presentation from XX mg to read "XX mg per capsule." As currently presented, it is unclear if the total contents of the sample blister card is XX mg or if the contents per capsule is XX mg. If a patient interprets XX mg as the total contents of the blister card instead of the contents of one capsule, an overdose error will occur.
3. Add a statement declaring the presence of FD&C Yellow No. 6 on the blister card labeling for the 50 mg, 100 mg, and 200 mg capsules per 21 CFR 201.20(c).
4. There should be sufficient drug information on all panels of the blister cards in the case that the blister cards are separated from each other. Add the proprietary name and established name to appear with the strength on Panels A, B, D, and E.
5. The blister card labeling designates a space for the package insert, but it does not designate a space for the placement of a pharmacy label. Indicate a designated space to affix the pharmacy prescription label.

D. (b) (4)

(b) (4)

E. Medication Guide

1. Negative warnings, such as "do not do that" can be misread as an affirmative warning "do this." [3] An affirmative warning should preface the negative warning to prevent misinterpretation. Consider revising the statement "TRADENAME may not be sprinkled on food, crushed, or chewed. Swallow capsule whole and intact." to read "**Swallow capsule whole and intact.** TRADENAME may not be sprinkled on food, crushed, or chewed."

2. To help distinguish this extended-release product from the marketed immediate-release topiramate products, consider adding a statement that this product is only administered once daily.

F. Insert Labeling

1. The symbols (b) (4) These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol, and the abbreviation (b) (4) can be misinterpreted as (b) (4) (b) (4)

2. When presenting numbers with symbols or units, insert a space between the number and the symbol, or unit, to provide better readability. Additionally, remove the symbol (b) (4) and insert the intended meaning. For example, in Section 2 Dosage and Administration, revise (b) (4) to read "50 mg per day."

3. We recommend adding a unit of measure immediately following all numbers, as appropriate. Additionally, remove the symbol (b) (4) and insert the intended meaning. For example, in Section 2 Dosage and Administration, revise (b) (4) to read "25 mg per day to 50 mg per day."

[3] Institute for Safe Medication Practices (ISMP). August 12, 2010. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Medication Safety Alert, 15(16).

4. The information found under Section 5.16 Swallow Capsule Whole and Intact should be relocated to Section 2 Dosage and Administration. Since negative warnings, such as "do not do that" can be misread as an affirmative warning, "do this,"[3] an affirmative warning should preface the negative warning to prevent misinterpretation. Consider revising the statement "Do not sprinkle on food, chew, or crush. Swallow capsule whole and intact." to read "Swallow capsule whole and intact. Do not sprinkle on food, chew, or crush."

(b) (4)

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Appendix E: ISR numbers of cases discussed in this review

7842142	7737244	3678251
4427472	7737245	5033802
6338791	7742843	6054235
7642211	7737246	7289166
5514285	7737243	7018211
4660664	4138599	7213442
6101473	4401927	7953657
5674763	4166980	7201332
4332550	4188525	
5905501	5328733	

Appendix F: ISR numbers of cases excluded in this review

4290381	5819482	7212462
4734705	5838681	7224770
4735824	6186721	7270547
4900416	6187924	7525363
4918493	6194717	7628554
4939430	6218038	7638106
4941905	6231052	7644147
5081911	6259600	7649071
5160706	6315030	7685432
5478111	6335184	7741854
5478113	6341682	7743287
5488076	6356686	7788933
5731605	6383244	7808378
5731606	6405809	7878412
5754122	6735116	6283317
5803932	6796211	6249171

6401263
4940990
5506860
6406378
6419413
6422714
6457599
6479491
6545988
6644228
6660582

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/s/

JULIE V NESHIEWAT
05/17/2012

IRENE Z CHAN
05/17/2012

KELLIE A TAYLOR
05/18/2012

CAROL A HOLQUIST
05/18/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**May 09, 2012**
To:	Russell Katz, MD, Director **Division of Neurology Products (DNP)**
Through:	Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	topiramate
Dosage Form and Route:	Extended-release Capsules, for Oral Use
Application Type/Number:	NDA 201635
Applicant:	**Supernus Pharmaceuticals**

1 INTRODUCTION

On January 14, 2011, the Applicant submitted for the Agency's review a New Drug Application (NDA 201635) for topiramate Extended-release Capsules, indicated for the treatment of certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people (b) (4) and for use with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children (b) (4) On March 14, 2011, DNP issued a Refuse to File (RTF) letter and on August 30, 2011, the Applicant resubmitted the NDA for topiramate Extended-release Capsules.

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for topiramate Extended-release Capsules.

Topiramate was originally approved on December 24, 1996 for:

- the treatment of certain types of seizures (partial onset seizures and primary generalized tonic-clonic seizures) in people 4 years and older,
- use with other medicines to treat certain types of seizures (partial onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 4 years and older,
- the prevention of migraine headaches in adults.

2 MATERIAL REVIEWED

- Draft topiramate Extended-release Capsules Medication Guide (MG) received on September 09, 2011, and received by DMPP on May 08, 2012.
- Draft topiramate Extended-release Capsules Prescribing Information (PI) received on September 09, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on May 08, 2012.
- Approved TOPAMAX (topiramate) comparator labeling dated July 15, 2011.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
05/09/2012

MELISSA I HULETT
05/10/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 21, 2012

TO: Russell G. Katz, M.D.
Director, Division of Neuropharmacology Products

FROM: Michael F. Skelly, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIRs Covering NDA 201-635, Topiramate ER Capsules, Sponsored by Supernus Pharmaceuticals, Inc.

At the request of the Division of Neuropharmacology Products (DNP) and the Office of Clinical Pharmacology, the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following studies:

Study 539P103: "A phase-I, single-center, multi-dose, randomized, single-blind, two-treatment crossover study to determine the pharmacokinetic profile of SPN-538 (topiramate Controlled-Release) Capsules relative to Topamax® tablets in healthy adult volunteers"

Clinical Site: Quintiles Phase I Unit
Overland Park, KS

Study 538P106-200: "A single-center, single-dose, open-label, randomized, two-treatment, two-period, two-sequence, crossover relative bioavailability study of Topiramate Extended-Release (TPM-XR) 200 mg capsules in healthy adult volunteers under fasting conditions"

Clinical Site: Dedicated Phase I, Inc. (now closed)
Phoenix, AZ

Study 538P106: "A single-center, single-dose, open-label, randomized, two-period, two-treatment, two-sequence crossover relative bioavailability study of Topiramate Controlled-Release (TPM-CR) 100 mg capsules in healthy adult volunteers under fasting conditions"

and

Study 538P106-50: "A single-center, single-dose, open-label, randomized, two-treatment, two-period, two-sequence, crossover relative bioavailability study of Topiramate Extended-Release (TPM-XR) 50 mg capsules in healthy adult volunteers under fasting conditions"

Clinical Site: PAREXEL International
Baltimore, MD

Analytical Site: Supernus Pharmaceuticals, Inc.
Rockville, MD

The inspections of the clinical portions were conducted at Quintiles, Overland Park, KS (study 538P103; 3/6-3/9/12); Bell Road Business Center, Phoenix, AZ (study 538P106-200; 3/12-3/16/12); and PAREXEL International, Baltimore, MD (studies 538P106 and 538P106-50; 1/4-1/10/12). The inspection of the analytical portions was conducted at Supernus Pharmaceuticals, Rockville, MD (four studies; 2/6-2/9/12).

Following the inspections, Form FDA-483 was issued only at Bell Road Business Center, to the former proprietor of Dedicated Phase I. The observation and our evaluation follow.

1) **The final protocol dated 14 Sep 2010 Page 20 of 39 states that serial blood samples (PK) will be taken from the dosed (one dose on day 1 and one dose on day 19) subjects at the following time intervals expressed in hours: 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 48, 72 and 96. The 2 hour blood sample was not taken on day 19 for the subject 110.**

The study report (p. 35) revealed that sampling times were not recorded at a single sampling time for three subjects, including #110 (P2-2h), #120 (P2-2h), and #132 (P2-36h). The actual time does not appear in Listing 16.2.6.1 of the final report for these subjects, but plasma samples for the scheduled times resulted in measured concentrations of topiramate. The scheduled times are well-separated from t_{max}. The measured concentrations and undocumented times are unlikely to influence

C_{max}, AUC, or AUC_{∞} parameters and bioequivalence assessments, whether or not the observations are used in calculations.

Conclusions:

Following the inspections, DBGC recommends the following:

- The OCP reviewer should judge the impact of the three undocumented pharmacokinetic sampling times.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly , Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classifications:

NAI - Quintiles Phase 1 Unit, Overland Park, KS
FEI: 3006737338

VAI - Dedicated Phase 1, Phoenix, AZ
FEI: 3009443882

NAI - PAREXEL International, Baltimore, MD
FEI: 3005445577

NAI - Supernus Pharmaceuticals, Rockville, MD
FEI: 3005209462

cc:
OSI/Ball/Moreno
OSI/DBGC/Taylor/Haidar/Skelly/Dejernett
OND/DNP/Ware
OCP/DCPI/Wu/Men
HFR-SW3515/Mueller
HFR-PA2530/Kapsala
HFR-CE250/McFiren
HFR-CE250/Harris
CDER DSI PM TRACK
Draft: MFS 3/20/2012
Edit: SHH 3/20/2012
DSI: BE6278; O:\Bioequiv\EIRCover\201635.sup.top.doc
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/s/

MICHAEL F SKELLY
03/21/2012

SAM H HAIDAR
03/23/2012

WILLIAM H TAYLOR
03/23/2012

Reference ID: 3424690

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 23, 2011

TO: Director, Investigations Branch
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215

Director, Investigations Branch
Kansas District Office
11630 West 80th St.
Lenexa, KS 66214

Director, Investigations Branch
Los Angeles District Office
19701 Fairchild
Irvine, CA 92612

From: Sam H. Haidar, R.Ph., Ph.D. _____
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data Validation Inspection** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 201635
DRUG: Topiramate CR Capsules
25 mg, 50 mg, 100 mg, 200 mg
SPONSOR: Supernus Pharmaceuticals, Inc.
Rockville, MD

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence studies. **A DBGC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGC upon receipt of this assignment to arrange scheduling of the analytical inspection. These inspections should be completed before February 20, 2011.**

Study Number: **538P103**
Study Title: "A phase-I, single-center, multi-dose, randomized, single-blind, two-treatment crossover study to determine the pharmacokinetic profile of SPN-538 (topiramate Controlled-Release) Capsules relative to Topamax® tablets in healthy adult volunteers"
Clinical Site: Quintiles Phase I Unit
6700 West 115th Street
Overland Park, Kansas 66211
TEL: (913)708-7555; (913)708-6000
FAX: (913)708-7607
Investigator: Phillip Leese, M.D.

Study Number: **538P106-200**
Study Title: "A single-center, single-dose, open-label, randomized, two-treatment, two-period, two-sequence, crossover relative bioavailability study of Topiramate Extended-Release (TPM-XR) 200 mg capsules in healthy adult volunteers under fasting conditions"
Clinical Site: Dedicated Phase I, Inc.
734 W Highland Ave
Phoenix, AZ 85013
TEL: (602)279-7300
Investigator: Kyle Patrick, DO

Study Number: **538P106**
Study Title: "A single-center, single-dose, open-label, randomized, two-period, two-treatment, two-sequence crossover relative bioavailability study of Topiramate Controlled-Release (TPM CR) 100 mg capsules in healthy adult volunteers under fasting conditions"

and
Study Number: **538P106-50**
Study Title: "A single-center, single-dose, open-label, randomized, two-treatment, two-period, two-sequence, crossover relative bioavailability study of Topiramate Extended-Release (TPM-XR) 50 mg capsules in healthy adult volunteers under fasting conditions"
Clinical Site: PAREXEL International
Early Phase Clinical Unit (EPCU)
Harbor Hospital Center, 7th Floor
3001 South Hanover Street

Baltimore, MD 21225
TEL: (410)350-3142; (410)350-7979
FAX: (410)354-4281

Investigator: Azra Hussaini, M.D.

Note: The Dedicated Phase I site may have closed.[1] However, some press inquiries about the bankruptcy have been answered by the proprietor's wife, who operates nearby Dedicated Clinical Research.[2][3] She may be able to facilitate access to records from Dedicated Phase I.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the site. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings.

Please check the batch numbers of the test and reference products used in these studies with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. The sites conducting the above bioequivalence studies are responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UC

[1] http://www.azcentral.com/business/abg/articles/2011/05/26/20110526abg-bankrupt0526 html
[2] http://www.dedicatedcr.com/content/CW%20Weekly%20-%20Profile%20Phase%20IIIa%20Unit%20-%20Phase%20II-IV%20Contract%20Research%20Organization.pdf
[3] http://www.dedicatedcr.com/contact.php

M126836.pdf). Samples of the test and reference products should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Custom house Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator (CI) or the responsible person at each CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and shipped them to DPA under current program directives. Please see the IOM and/or contact your district or DFFI for assistance with the Sample Collection Report.

Analytical Site: Supernus Pharmaceuticals, Inc.
Bioanalytical laboratory
1550 East Gude Dr.
Rockville, MD 20850
TEL: (301)838-2500
FAX: (301)424-1364

Investigators: Megan E. Greenwell, M.S. (Study 538P103)
Matthew N. McQueen (Study 538P106-200)
Nicholas D. Fry (Study 538P106)
Jeremy A. Hiatt (Study 538P106-50)

Methodology: LC-MS/MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the site. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. **The SOP(s) for repeat assays and other relevant**

procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Jyoti B. Patel, Ph.D.
(301) 796-4617
jyoti.patel@fda.hhs.gov

CC:
CDER OSI PM TRACK
OSI/DBGC/Salewski/Haidar/Skelly/Patel/Dejernett/CF
OND/ODEI/DNP/Ware
OTS/OCP/DCPI/Wu/Men
HFR-PA2535/Maxwell (DIB)/Hall (BIMO)
HFR-SW350/Bromley Jr. (DIB)/Montgomery/Stevens (BIMO)
HFR-CE250/Smith (DIB)/Harris (BIMO)
Draft: JBP 12/23/2011
Edit: MFS 12/23/2011
OSI File # 6278; O:\BE\assigns\bio201635.doc
FACTS: **1369811**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JYOTI B PATEL
12/23/2011

MICHAEL F SKELLY
12/23/2011
Skelly signing on behalf of Dr. Haidar

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 201635 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: topiramate Dosage Form: extended release capsules Strengths: 25 mg, 50 mg, 100 mg, 200 mg		
Applicant: Supernus Pharmaceuticals Inc. Agent for Applicant (if applicable): n/a		
Date of Application: January 13, 2011 Date of Receipt: January 14, 2011 Date clock started after UN: n/a		
PDUFA Goal Date: November 14, 2011	Action Goal Date (if different): n/a	
Filing Date: March 14, 2011	Date of Filing Meeting: February 22, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): • Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS). • Initial monotherapy in patients greater than or equal to 10 years of age with partial onset or primary generalized tonic-clonic seizures.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? NO ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 101670	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified: ✓				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	✓			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
N020505	Topamax (topirmate) Tablets	M-54	December 22, 2012
N020505	Topamax (topiramate) Tablets	PED	June 22, 2013

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*		✓		

Exclusivity (continued)	YES	NO	NA	Comment
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			✓	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			✓	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			eCTD backbone
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			✓	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***		✓		Requested in NDA acknowledgement letter
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and***	✓			

the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			✓	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			✓	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	✓			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		(b) (4)
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		✓		(b) (4)

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			✓	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		✓		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	✓			Submitted under IND 101670; OSE has spoken with firm and requested submission under NDA
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***	✓			Same as Topamax under NDA 20505
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	✓			
Is the PI submitted in PLR format?[4]	✓			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				To do
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				To do
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				To do
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				Confirm at filing if needed.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 15, 2009 (DNP) & April 26, 2010 (CMC only) ***If yes, distribute minutes before filing meeting***	✓			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date:** September 2, 2010 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		✓		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 22, 2011

BLA/NDA/Supp #: 201635

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: topiramate extended release

DOSAGE FORM/STRENGTH: capsules

APPLICANT: Supernus

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- Adjunctive therapy for adults and pediatric patients (b) (4) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS).
- Initial monotherapy in patients greater than or equal to 10 years of age with partial onset or primary generalized tonic-clonic seizures.

BACKGROUND:

Supernus Pharmaceuticals has developed an extended release (XR) capsule formulation of topiramate. In the current 505(b)(2) NDA, the firm proposes marketing topiramate XR capsules for adjunctive therapy of epilepsy in patients (b) (4) and for monotherapy of epilepsy in patients 10 years of age and older. Four strengths are proposed, 25 mg, 50 mg 100 mg and 200 mg. The recommended dose for adjunctive therapy is 200 mg/day to 400 mg/day in adults and 5-9 mg/kg/day in pediatric patients (b) (4) The recommended dose for monotherapy is 400 mg/day. The firm is not seeking an indication for migraine prophylaxis, which is still protected by the innovator's patent.

Topiramate was originally developed by Ortho McNeil/Janssen Pharmaceuticals (Ortho) for treatment of epilepsy. The innovator product, Topamax® (topiramate) Tablets (the RDL) was approved under NDA 20-505 in 1996. Currently Ortho markets Topamax® Tablets 25 mg, 50 mg, 100 mg, and 200 mg for treatment of epilepsy and prophylaxis of migraine. Ortho also markets Topamax® (topiramate) Sprinkle Capsules 15 mg and 25 mg for the same indications.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jackie Ware	Y
	CPMS/TL:	Robbin Nighswander	N
Cross-Discipline Team Leader (CDTL)	Angela Men		Y
Clinical	Reviewer:	Martin Rusinowitz	Y
	TL:	Norman Hershkowitz	Y

Clinical Pharmacology	Reviewer:	Ta-Chen Wu	Y
	TL:	Angela Men	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ed Fisher	N
	TL:	Lois Freed	Y
Product Quality (CMC)	Reviewer	Thomas Wong	Y
	TL:	Martha Heimann Ramesh Sood	Y Y
OSE	RPM:	Laurie Kelly	Y
Bioresearch Monitoring (DSI)	Reviewer:	Mike Skelley	Y
Other attendees:	Kelly Summers, Safety RPM, DNP Arzu Selen, Biopharmaceutics Reviewer Angelica Dorantes, Biopharmaceutics TL Mildred Wright, PMHS Diem-Kieu Ngo, AC Staff Colleen Locicero, ODE I Jeanine Best, PMHS Kendra Biddick, CDER OC		Y Y Y Y Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: none	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical study site(s) inspections(s) needed? **If no,** explain: No clinical efficacy studies were submitted.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: This drug is not the first in its class.
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Will request PK parameters dataset	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO

BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: See filing reviews for details	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☒ Not applicable ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority:

21st Century Review Milestones:

Stamp Date: January 14, 2011
Filing Date: March 15, 2011
Day 74 Letter Date: March 29, 2011

Review completion Goal Date according to GRMP: 09/04/2011
Primary reviewer to TL: October 10, 2011
Primary TL to CDTL: October 17, 2011 **CDTL – Hershkowitz??**
CDTL to DD: October 24, 2011

PDUFA Goal Date: November 14, 2011

Mid-Cycle meeting date: TBD (target date: June 14, 2011)
Wrap-up meeting date: TBD (target date: October 10, 2011)

Proposed Labeling/PMC/PMR/REMS to sponsor: October 17, 2011

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☒	The application is unsuitable for filing. Explain why: See CMC and biopharmaceutics filing reviews.
☐	The application, on its face, appears to be suitable for filing.

	Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☒	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE H WARE
09/08/2011